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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/796,323	COLE ET AL.	
	Examiner	Art Unit	
	Stephanie K. Mummert, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on October 16, 2006 is acknowledged and has been entered. Claims 1, 22, 24 have been amended. Claims 31-37 have been canceled. Claims 1-30 are pending.

Claims 1-30 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on October 17, 1006 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 14, 16-18, 22-23, 25 and 31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6, 20 and 24 of copending Application No. 10/951,983 ('983 herein) in view of McCarthy et al. (US PgPub 2004/0067559; April 2004). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and the copending application are nearly identical in the components/reagents and recited method steps claimed within the copending applications.

The difference(s) between the claims of the instant application and the '983 application is primarily seen in the different manner in which the limitations of the related methods are claimed. For example, in the instant application, the method of claim 1 includes steps directed towards the synthesis of cDNA in the presence of dUTP, while the copending application refers generally to synthesizing cDNA in the presence of a modified DNA precursor in claim 1, with dependent claim 2, limiting the precursor to dUTP.

This same issue arises for other limitations within claim 1 of the '983 application which are found in dependent limitations in the instant application. For example, claim 1 of '983 application claims a step of cleaving the cDNA at abasic sites followed by labeling the fragments with biotin and hybridizing the fragments to a microarray of probes. These same limitations are claimed in the instant application, but these limitations are claimed in dependent claims 16-17 where the fragments are labeled and may be labeled with biotin, and claims 22-23 and 31 where the fragments are labeled and hybridized to an array of probes.

The major difference between the claims of the copending application and the instant application lies in the final step of the method, where the free 3'OH is labeled using a terminal transferase in the copending application, while the free 3'OH is extended by a strand displacing polymerase in the method of the instant application. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the technique of cDNA synthesis, fragmentation, and labeling taught by Blume to include the step taught by McCarthy, where the free 3'OH termini are extended using a strand displacing polymerase. As taught by McCarthy, "The method according to the invention provides a means of generating multiple copies of discrete single stranded primers downstream of an initiating primer. This offers exceptional specificity for detection purposes, as the discrete downstream primers can only be generated if the target template nucleic acid is present" (p. 5, paragraph 71). Given the benefit of specificity in detection provided by the method taught by McCarthy, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the step of extending the free 3'OH using a strand displacing polymerase for the step of labeling

using a terminal transferase as taught by Blume with a reasonable expectation for success to achieve improved specificity for detection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENT TO THE CLAIMS

Claim Rejections - 35 USC § 103

6. Claims 1-10, 12-16, 18-20, 24-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghosh et al. (Developmental Brain Research 1997, vol. 102, p. 1-12) and McCarthy et al. (US PgPub 2004/0067559; April 2004). Ghosh teaches an analysis of gene expression which includes cDNA synthesis and amplification of cDNA samples (Abstract).

With regard to claim 1, Ghosh teaches a method of amplifying RNA in a nucleic acid sample to obtain sense strand cDNA fragments comprising:

a) obtaining a nucleic acid sample comprising RNA (p. 2, 'RNA extraction' heading, where total RNA was extracted from tissue samples);

b) contacting the nucleic acid sample with the appropriate reagents to synthesize a first strand cDNA using the RNA as a template (p. 2, 'synthesis of the first strand cDNA from total RNA' heading, where first strand cDNA was synthesized using the total RNA as a template, with oligo(dT) primer used to initiate cDNA synthesis);

c) synthesizing a second strand cDNA, using said first strand cDNA as a template (p. 2, 'second strand cDNA synthesis' heading, where second strand cDNA was synthesized by incubating the first strand mixture with second strand buffer).

With regard to claim 9, Ghosh teaches an embodiment of claim 1, wherein the first strand cDNA is synthesized in the presence of an RNA dependent DNA polymerase (p. 2, 'synthesis of first strand cDNA from total RNA' heading, where the synthesis is in the presence of reverse transcriptase, an RNA dependent DNA polymerase) and second strand cDNA is synthesized in the presence of a DNA dependent DNA polymerase (p. 2, 'second strand cDNA synthesis' heading, where synthesis occurs in the presence of DNA polymerase).

With regard to claim 18, Ghosh teaches an embodiment of claim 1, wherein the first strand cDNA is synthesized by a method comprising: hybridizing at least one primer to the nucleic acid sample and extending the primer with a polymerase (p. 2, 'synthesis of the first strand cDNA from total RNA' heading, where first strand cDNA was synthesized using the total RNA as a template, with oligo(dT) primer used to initiate cDNA synthesis).

With regard to claim 19, Ghosh teaches an embodiment of claim 18, wherein the nucleic acid sample comprises RNA and the polymerase is an RNA dependent DNA polymerase (p. 2, 'synthesis of first strand cDNA from total RNA' heading, where the synthesis is in the presence of reverse transcriptase, an RNA dependent DNA polymerase).

With regard to claim 20, Ghosh teaches an embodiment of claim 18, wherein the at least one primer comprises a 3' oligo dT portion (p. 2, 'synthesis of the first strand cDNA from total RNA' heading, where first strand cDNA was synthesized using the total RNA as a template, with

a primer comprising an oligo(dT) portion preceded by T7 promoter sequence is used to initiate cDNA synthesis).

With regard to claim 24, Ghosh teaches an embodiment of l, wherein first strand cDNA is synthesized using an RNA dependent DNA polymerase (p. 2, 'synthesis of first strand cDNA from total RNA' heading, where the synthesis is in the presence of reverse transcriptase, an RNA dependent DNA polymerase).

With regard to claim 25, Ghosh teaches an embodiment of claim 20, wherein first strand cDNA is synthesized by a primer comprising oligo dT (p. 2, 'synthesis of the first strand cDNA from total RNA' heading, where first strand cDNA was synthesized using the total RNA as a template, with a primer comprising an oligo(dT) portion preceded by T7 promoter sequence is used to initiate cDNA synthesis).

Regarding claim 1, Ghosh does not teach steps d) and e) comprising steps directed to synthesizing the second strand of cDNA in a reaction comprising dUTP, nicking the second strand cDNA at one or more positions where dUTP was incorporated and extending the second strand cDNA from one or more nicks in the mixture using a strand displacing DNA polymerase.

McCarthy teaches a method for amplification of a template nucleic acid through primer extension, cleavage of modified nucleotides, and extending the 3'-OH generated by the cleavage (Abstract).

Regarding claim 1, McCarthy teaches steps c) to e) as follows:

c) synthesizing a second strand cDNA comprising UTP, using said first strand cDNA as a template in a reaction mixture comprising dUTP (p. 3, paragraphs 32-39, where a primer is extended in the presence of at least one modified DNA precursor which is a substrate for a DNA

glycosylase; p. 4, paragraphs 49-55, where the modified DNA precursor is dUTP; p. 6, paragraph 91-102; see also p. 13-14, example 1, paragraph 167-168, where the reaction included 0.2 mM each of dATP, dGTP, dUTP and 0.02 mM dCTP and α^{32}PdCTP);

d) nicking the second strand cDNA at one or more portions where dUTP was incorporated to generate one or more nicks (p. 4, paragraphs 49-59, where the modified dUTP is excised by uracil DNA-glycosylase (UDG) and where the cleavage of the abasic site is by Endonuclease IV; p. 6, paragraphs 91-102; see also p. 13-14, example 1, paragraph 168, where the reaction was dropped to 37°C and 5 units of Klenow fragment (3'-5' exo-), 1 unit of E. coli Uracil DNA glycosylase were added along with 2 units of Endonuclease IV); and

e) extending the second strand cDNA from the one or more nicks in a reaction mixture comprising dUTP and a DNA polymerase with a strand displacing activity, wherein downstream fragments of the second strand cDNA are displaced (p. 6, paragraph 102, where the DNA polymerase synthesizes new DNA from the 3'OH termini and displaces the downstream DNA; p. 3, paragraph 32-39, where the free 3;OH generated by the cleavage at the abasic site is extendable by the DNA polymerase; see also p. 13-14, example 1, paragraph 168-169) to obtain sense strand cDNA fragments from said RNA (p. 3, paragraph 39, where it is noted that the template strand can be any strand from a natural or artificially synthesized nucleic acid, therefore it would have been prima facie obvious to apply the dUTP and UDG cleavage to sense strand cDNA fragments generated from said RNA sample).

With regard to claim 2, McCarthy teaches an embodiment of claim 1 wherein steps d) and e) are performed simultaneously in a single reaction (p. 6, paragraph 96, where it is noted that the steps cycle continuously until one of the reagents becomes limiting; p. 6, paragraph 98,

where the components of the reaction are all simultaneously present in the same reaction and a continuous cycle of extension and cleavage results in the amplification of multiple copies of displaced downstream fragments).

With regard to claim 3, McCarthy teaches an embodiment of claim 1, wherein step d) comprises: generating abasic sites in the second strand cDNA and cleaving the second strand cDNA at the abasic sites (p. 4, paragraphs 49-59, where the modified dUTP is excised by uracil DNA-glycosylase (UDG) and where the cleavage of the abasic site is by Endonuclease IV).

With regard to claim 4, McCarthy teaches an embodiment of claim 3, wherein the abasic sites are generated by incubating with a uracil DNA glycosylase enzyme (p. 4, paragraphs 49-59, where the modified dUTP is excised by uracil DNA-glycosylase (UDG) and where the cleavage of the abasic site is by Endonuclease IV).

With regard to claim 5, McCarthy teaches an embodiment of claim 3, wherein the step of cleaving the second strand cDNA at the abasic sites comprises incubating the second strand cDNA with an apurinic endonuclease (p. 4, paragraphs 49-59, where the modified dUTP is excised by uracil DNA-glycosylase (UDG) and where the cleavage of the abasic site is by Endonuclease IV).

With regard to claim 6, McCarthy teaches an embodiment of claim 5, wherein the apurinic endonuclease is Endonuclease IV (p. 4, paragraphs 49-59, where the modified dUTP is excised by uracil DNA-glycosylase (UDG) and where the cleavage of the abasic site is by Endonuclease IV).

With regard to claim 7, McCarthy teaches an embodiment of claim 3, wherein the step of cleaving the second strand cDNA at abasic sites comprises incubating the second strand cDNA at

high temperatures (p. 4, paragraph 59, where agents which cleave 3' to the phosphate moiety to generate a 3' terminus which a 3'-P group are heat, alkali and DNA repair enzymes).

With regard to claim 8, McCarthy teaches an embodiment of claim 3, wherein the step of cleaving the second strand cDNA at abasic sites comprises incubating the second strand cDNA under alkaline conditions (p. 4, paragraph 59, where agents which cleave 3' to the phosphate moiety to generate a 3' terminus which a 3'-P group are heat, alkali and DNA repair enzymes).

With regard to claim 10, McCarthy teaches an embodiment of claim 1, wherein the strand displacing DNA polymerase is selected from the group consisting of the Klenow fragment, Bst and phi29 (p. 13-14, example 1, paragraph 168, where the reaction was dropped to 37oC and 5 units of Klenow fragment (3'-5' exo-), 1 unit of E. coli Uracil DNA glycosylase were added along with 2 units of Endonuclease IV).

With regard to claim 12, McCarthy teaches an embodiment of claim 1, wherein steps d) and e) are performed under isothermal conditions (p. 13-14, example 1, paragraph 168, where the reaction was dropped to 37°C and 5 units of Klenow fragment (3'-5' exo-), 1 unit of E. coli Uracil DNA glycosylase were added along with 2 units of Endonuclease IV, where the reaction was carried out at 37°C).

With regard to claim 13, McCarthy teaches an embodiment of claim 1, wherein steps d) and e) are performed at 37°C (p. 13-14, example 1, paragraph 168, where the reaction was dropped to 37°C and 5 units of Klenow fragment (3'-5' exo-), 1 unit of E. coli Uracil DNA glycosylase were added along with 2 units of Endonuclease IV, where the reaction was carried out at 37°C).

With regard to claim 14, McCarthy teaches an embodiment of claim 1, wherein the Endonuclease V is used to nick the second strand cDNA in step d) (p. 4, paragraph 62, where it is noted that the 3' endonuclease may be Endonuclease V).

With regard to claim 15, McCarthy teaches an embodiment of claim 1, wherein the reaction mixture of step c) further comprises dTTP and the ratio of dTTP to dUTP in the starting mixture is greater than about 5 to 1 (p. 10-11, paragraph 138-139, where dTTP is included with a ratio of dUTP to generate fragments of multiple sizes).

With regard to claim 16, McCarthy teaches an embodiment of claim 1, wherein the reaction mixture of step e) further comprises a labeled nucleotide (p. 13-14, example 1, paragraph 167-168, where the reaction included 0.2 mM each of dATP, dGTP, dUTP and 0.02 mM dCTP and α^{32}PdCTP).

With regard to claim 27, McCarthy teaches an embodiment of claim 1, wherein the nucleic acid comprises genomic DNA (p. 9-10, paragraph 133-134, where genomic DNA can serve as the template for the GMA reaction).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the method of generation of abasic sites in a nucleic acid sample, followed by amplification of the displaced downstream fragments through cycling of the primer extension, cleavage and extension process described above into a method of cDNA synthesis as disclosed by Ghosh, methods which are well known in the prior art at the time the invention was made. McCarthy explicitly teaches "When an RNA template is used, a DNA polymerase which can utilize an RNA template is required, typically such an enzyme is reverse transcriptase" (p. 3, paragraph 47), providing a direct teaching that the method can be applied to

RNA targets as part of reverse transcription. Furthermore, the method disclosed by McCarthy "provides a means of generating multiple copies of discrete single stranded primers downstream of an initiating primer. This offers exceptional specificity for detection purposes, as the discrete downstream primers can only be generated if the target template nucleic acid is present" (p. 5, paragraph 71)". McCarthy also notes that "the method according to the invention has significant advantages over existing technologies in that it is more versatile and more flexible with respect to providing a single high throughput process that can be easily adapted to multiple different formats in the fields of DNA detection, quantitation and characterization" (p. 3, paragraph 37). Finally, McCarthy also teaches "typically, the nucleic acid template strand can be any strand from a natural or artificially synthesized nucleic acid" (p. 3, paragraph 39). Therefore, given the benefit of specificity in detection provided by the method taught by McCarthy, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of glycosylase mediated amplification taught by McCarthy to a method of cDNA synthesis, as exemplified by Ghosh and to obtain sense strand cDNA fragments from said RNA with a reasonable expectation for success.

7. Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghosh et al. (Developmental Brain Research 1997, vol. 102, p. 1-12) and McCarthy et al. (US PgPub 2004/0067559; April 2004) as applied to claims 1-10, 12-16, 18-20, 24-25 and 27 above, and further in view of Blanco et al. (US Patent 5,198,543; March 1993). Ghosh teaches an analysis of gene expression which includes cDNA synthesis and amplification of cDNA samples (Abstract).

Ghosh in view of McCarthy teach the limitations of claims 1-10, 12-16, 18-20, 24-25 and 27 as recited in the 103 rejection stated above. However, Ghosh and McCarthy do not teach the use of a strand displacing DNA polymerase phi29 with decreased exonuclease activity. Blanco teaches an improved method for determining the nucleotide sequence of a DNA molecule (Abstract).

With regard to claim 10, Blanco teaches an embodiment of claim 1, wherein the strand displacing DNA polymerase is selected from the group consisting of the Klenow fragment, Bst and phi29 (Abstract, where the improvement is a modification of the phi29 DNA polymerase).

With regard to claim 11, Blanco teaches an embodiment of claim 1, wherein the DNA polymerase is a phi29 variant that has reduced exonuclease activity (col. 2, lines 43-49, where a phi29 modified to reduce exonuclease activity to less than 10% of naturally occurring phi29 polymerase is incorporated into the method).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the phi29 polymerase enzyme with reduced exonuclease activity as taught by Blanco into the method of modification of cDNA synthesis using the digestion/nicking method taught by McCarthy with a reasonable expectation for success. As noted by Blanco, "the invention provides a polymerase which is highly processive, and may be produced with a low exonuclease activity. The high processivity of the polymerase makes it suitable, not only for DNA sequencing, but also for amplification of very large fragments of DNA (in excess of 10 kilobases in length). This makes the polymerase useful in a polymerase chain reaction (PCR) type procedure or in replicative type, protein primed, extension reactions" (col. 3, lines 50-61). One of ordinary skill in the art at the time the invention was made would

have recognized the benefit of improved read-length provided by the modified phi29 polymerase and would have been motivated to substitute this strand displacing enzyme for the Klenow fragment taught by McCarthy for extension of the 3'OH termini which are crucial for the practice of the invention, and such modification would have a reasonable expectation for success.

8. Claims 17-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghosh et al. (Developmental Brain Research 1997, vol. 102, p. 1-12) and McCarthy et al. (US PgPub 2004/0067559; April 2004) as applied to claims 1-10, 12-16, 18-20, 24-25 and 27 above, and further in view of Wang et al. (US Patent 6,004,755; December 1999). Ghosh teaches an analysis of gene expression which includes cDNA synthesis and amplification of cDNA samples (Abstract).

Ghosh in view of McCarthy teach the limitations of claims 1-10, 12-16, 18-20, 24-25 and 27 as recited in the 103 rejection stated above. However, neither Ghosh nor McCarthy teach the inclusion of biotin as a detectable label.

Wang teaches the inclusion of biotin in cDNA synthesis as part of quantitative gene expression analysis (Abstract).

With regard to claim 17, Wang teaches an embodiment of claim 16, wherein the labeled nucleotide is biotin-dATP (col. 9, lines 20-28, where the labeled nucleotide is biotin).

With regard to claim 23, Wang teaches an embodiment of claim 21, wherein the label is biotin (col. 9, lines 20-28, where the labeled nucleotide is biotin).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the incorporation of biotin modified nucleotides into the cDNA synthesis technique taught by Ghosh and the method of fragmentation and amplification taught by McCarthy. The inclusion of a detectable label allows for specific detection of the hybridization pattern on the array and specifically when biotin is used as the label, "one contacts the array with streptavidin-fluorescer conjugate under conditions sufficient for binding between the specific binding member pairs to occur. Following contact, any unbound members of the signal producing system will then be removed, e.g., by washing" (col. 7, lines 11-22). Recognizing the specificity provided by the inclusion of a detectable label, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate a biotin label into the method taught by Ghosh and McCarthy with a reasonable expectation for success.

9. Claims 21-22 are rejected in view of Ghosh et al. (Developmental Brain Research 1997, vol. 102, p. 1-12) and McCarthy et al. (US PgPub 2004/0067559; April 2004) as applied to claims 1-10, 12-16, 18-20, 24-25 and 27 above and further in view of Golby et al. (Comparative Biochemistry and Physiology Part B, 2002, vol. 133, p. 537-542). Ghosh teaches an analysis of gene expression which includes cDNA synthesis and amplification of cDNA samples (Abstract).

With regard to claim 22, Ghosh in view of McCarthy teaches a method of detecting a target sequence in a nucleic acid sample comprising RNA, said method comprising:
a) amplifying the nucleic acid sample by the method of claim 1 ((see rejection under 103 stated above);

b) labeling the nucleic acids in the amplified nucleic acid sample with a detectable label (p. 13-14, example 1, paragraph 167-168, where the reaction included 0.2 mM each of dATP, dGTP, dUTP and 0.02 mM dCTP and α^{32}PdCTP);

Ghosh in view of McCarthy teaches the limitations of claims 1-10, 12-16, 18-20, 24-25 and 27 as recited in the 103 rejection stated above. However, neither Ghosh or McCarthy teaches the inclusion of primers comprising random sequence or the hybridization of labeled amplified nucleic acids to an array of probes. Golby teaches an analysis of gene expression using cDNA library arrays (Abstract).

With regard to claim 21, Golby teaches an embodiment of claim 18, wherein the at least one primer comprises a mixture of primers of random sequence wherein the primers are of a common length and the length is between 6 and 15 nucleotides (p. 538, col. 2, 'tracer synthesis' heading, where first strand cDNA was synthesized using a random hexameric primer, wherein a hexameric primer would comprise a primer of a common length of six nucleotides).

With regard to claim 22, Golby teaches a method of detecting a target sequence in a nucleic acid sample comprising RNA, said method comprising:

c) hybridizing the labeled, amplified nucleic acids to an array of probes comprising at least one probe that is perfectly complementary to the target sequence over the length of the probe (p. 541, col. 2, 'hybridization to arrays' heading, where hybridization is carried out);

d) detecting a hybridization pattern (p. 541, col. 2, 'hybridization to arrays' heading, where detection of the hybridized array spots is performed using a method appropriate for the label, eg by phosphorimager); and

e) determining if the target sequence is present or absent based on the hybridization pattern (p. 541, col. 2, 'hybridization to arrays' heading, where detection of the hybridized array spots is performed using a method appropriate for the label, e.g. by phosphorimager).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of the methods of Ghosh in view of McCarthy to incorporate the steps of hybridizing the cDNA sample to an array as taught by Golby to arrive at the claimed invention with a reasonable expectation for success. As taught by Golby, "the quickest and least costly method to produce DNA arrays from a clone library arrays in microplates is to use a robotic arrayer, or gridder, such as the Qbot (Genetix Ltd) to produce high density colony arrays on nylon membranes" (p. 537, col. 1). Golby also teaches "the arrays have a wide range of applications from simple library screening for a particular sequence to more complex applications such as gene expression analysis" and notes that "it can be used to identify potentially interesting genes, which could then be further analyzed by other techniques such as microarrays, real-time PCR and RT-PCR" (p. 538, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the steps of hybridization to an array and detection of the hybridization pattern as taught by Golby into the method of RNA amplification taught by a combination of Ghosh and McCarthy to achieve more high throughput and cost effective analysis of gene expression.

10. Claim 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghosh et al. (Developmental Brain Research 1997, vol. 102, p. 1-12), McCarthy et al. (US PgPub 2004/0067559; April 2004) and Wang et al. (US Patent 6,004,755; December 1999) as applied to

claims 17-23 above, and further in view of Sehgal et al. (Journal of Surgical Oncology, 1998, vol. 67, p. 234-241).

Ghosh in view of McCarthy teach the limitations of claims 1-10, 12-16, 18-20, 24-25 and 27 as recited in the 103 rejection stated above. However, neither Ghosh or McCarthy teach that the first strand cDNA synthesis is primed by a plurality of locus specific primers. Sehgal teaches a method of differential hybridization of cDNA expression arrays (Abstract).

With regard to claims 26 and 28, Sehgal teaches an embodiment of claims 20 and 23, wherein first strand cDNA synthesis is primed by a plurality of locus specific primers (p. 236, col. 2, 'gene specific primers' heading).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of the method of RNA amplification and fragmenting taught by a combination of Ghosh, McCarthy and Wang to include cDNA synthesis using gene specific primers to arrive at the claimed invention with a reasonable expectation for success. As taught by Sehgal, "to confirm the differential expression of genes identified on the expression array, we used the technique of gene-specific RT-PCR" (p. 236, col. 1). Sehgal also teaches "using the technique of gene-specific RT-PCR, we demonstrated that five of seven genes analyzed agree in their expression pattern as observed in Atlas ™ Human cDNA expression arrays" (p. 241, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate gene specific primers into the method of cDNA synthesis taught by Ghosh, McCarthy and Wang to incorporate the gene specific cDNA synthesis of Seghal to achieve more reliable and confirmed expression results following the more high-throughput analysis provided using array hybridizations.

11. Claims 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghosh et al. (Developmental Brain Research 1997, vol. 102, p. 1-12) and McCarthy et al. (US PgPub 2004/0067559; April 2004) as applied to claims 1-10, 12-16, 18-20, 24-25 and 27 above, and further in view of Caskey et al. (US Patent 5,364,759; November 1994). Ghosh teaches an analysis of gene expression which includes cDNA synthesis and amplification of cDNA samples (Abstract).

Ghosh in view of McCarthy teach the limitations of claims 1-10, 12-16, 18-20, 24-25 and 27 as recited in the 103 rejection stated above. However, neither Ghosh or McCarthy teach the inclusion of biotin as a detectable label.

With regard to claim 29, Caskey teaches an embodiment of claim 1, wherein the nucleic acid sample comprises adaptor ligated DNA fragments (col. 10, example 3, where a linker of non-complementary DNA is ligated to the population of blunt-ended molecules).

With regard to claim 30, Caskey teaches an embodiment of claim 1, wherein the nucleic acid sample comprises adaptor ligated DNA fragments that have been amplified by PCR (col. 10, example 3, where a linker of non-complementary DNA is ligated to the population of blunt-ended molecules and the samples are amplified by PCR).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the adaptor ligated PCR amplification fragments disclosed by Caskey into the method of DNA detection and characterization disclosed by Ghosh and McCarthy. As noted by Caskey, "this assay incorporates internal or external standards, provides higher sensitivity, requires shorter analysis time, lowers expense, and enables precise

identification of alleles". Therefore, given the benefit of a more rapid method, with greater precision and sensitivity one of ordinary skill in the art would have been motivated to include the adaptor ligation method taught by Caskey as a target nucleic acid for the method taught by Ghosh and McCarthy with a reasonable expectation for success.

Response to Arguments

Applicant's arguments with respect to claims 1-30 have been considered but are moot in view of the new ground(s) of rejection.

With regard to the rejection under provisional double patenting, Applicant's arguments are fully considered and found unpersuasive because it is not the only remaining rejection in this application. As discussed above, the rejections under 35 U.S.C. 103(a) are still pending. Thus, the rejection under provisional double patenting is maintained until the issues are resolved.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Porat et al. (US PgPub 2004/0166493; August 2004) teaches a method for identifying variations, such as single nucleotide polymorphisms (Abstract).

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephanie K. Mummert

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Examiner
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